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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/927,458	08/13/2001	David Wallach	WALLACH=22A	6865

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EXAMINER
HUYNH, PHUONG N

ART UNIT	PAPER NUMBER
1644	10

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/927,458	Applicant(s) WALLACH ET AL.	
	Examiner " Neon" Phuong Huynh	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 December 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-16,18-20 and 27-29* is/are pending in the application.

4a) Of the above claim(s) *18-20 and 27-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13 and 15-16* is/are rejected.

7)☒ Claim(s) *14* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 13-16, 18-20 and 27-29 are pending.

2. The request that antibody of claims 18-19, and 28 should be examined with the elected polypeptide of claims 13-16 and once the polypeptide claims are found to be allowable, the method of use in claims 20, 27 and 29 should also be examined in this case. This is not found persuasive because of the reasons set forth in the restriction mailed 5/6/02 and Office Action mailed 7/16/02. Inventions of Groups III and IV are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, the **antibody and polypeptide** as claimed differ with respect to their structure and physiochemical properties. Therefore, they **are patentably distinct**. As pointed out previously, antibody and polypeptide are drawn to different class and subclass. A search of one would not encompass the other. It is a burden to search more than one invention. With regard to obviousness between antibody and protein, a protein may appear to be obvious for making the antibody, providing that polypeptide is known. However, the protein may not be obvious to make from the antibody because of cross-reactivity, conformational dependency of antibody that depends upon how the antibody is made, for example, from a peptide or from a full-length polypeptide, the antigenic determinant of the antibody, etc. Further, the issuance of a patent for the claimed antibody that binds to the claimed polypeptide would not be obvious and provide coverage for the polypeptide and vice versa. In short, there is no double patenting issue between the antibody and the polypeptide. With regard to method claims, this is a US case CIP of 09/381,358 and not a straight 371 of PCT/IL98/00125 filed 3/19/1998. Therefore, the requirement of Group III and Groups I-II and IV-VII is still deemed proper and is therefore made FINAL.

3. Newly submitted claim 29 directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: claim 29 (Group V of restriction), drawn to a method of modulating cellular processes using polypeptide, class 435, subclass 183. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits.

Accordingly, claim 29 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

4. Claims 18-20 and 27-29 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

5. The enablement rejection of claims 13 and 15-16 under 35 U.S.C. 112, first paragraph is hereby withdrawn in view of the depository receipt and the statement that all restrictions placed on the deposit will be irrevocably removed upon granting a patent, filed 12/16/02 by David Wallach Ruth Granoth and Yaacov Cohen.

6. The following new grounds of rejection are necessitated by the amendment filed 12/16/02.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 13 and 15-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) an isolated polypeptide comprising SEQ ID NO: 2 which is capable of binding to receptor interacting protein (RIP) and inhibits the Jun kinase induction in vitro or a RIP-associated protein (RAP) encoded by a DNA sequence in a clone deposited with Collection Nationale de Cultures de Microorganisms under accession number I-2706 which is capable of binding to receptor interacting protein (RIP) and inhibits the Jun kinase induction in vitro, **does not** reasonably provide enablement for (1) *any* fragment of a RIP-associated protein (RAP) encoded by a DNA sequence in a clone deposited with Collection Nationale de Cultures de Microorganisms under accession number I-2706 which binds to RIP, (2) *any* "analog" of a RIP-associated protein (RAP) encoded by a DNA sequence in a clone deposited with Collection Nationale de Cultures de Microorganisms under accession number I-2706 "having no more than ten changes in said amino acid sequence, each said change being a substitution, deletion, or insertion of an amino acid", which analog binds to RIP; (3) *any* "derivative" of RIP-associated protein (RAP) encoded by a DNA sequence in a clone deposited with collection Nationale de Cultures de Microorganisms under accession number I-2706 or *any* fragment thereof which binds

to RIP, or any "analog" of a RIP-associated protein (RAP) encoded by a DNA sequence in a clone deposited with Collection Nationale de Cultures de Microorganisms under accession number I-2706 "having no more than ten changes in said amino acid sequence, each said change being a substitution, deletion, or insertion of an amino acid", which analog binds to RIP by modification of any functional group which occurs as a side chain or any N- or C-terminal group of any one or more amino acid residues thereof without changing one amino acid to another of the twenty commonly-occurring natural amino acids, which derivative binds to RIP, (4) *any* polypeptide mentioned above which "comprises any fragment of a RIP-associated protein (RAP) encoded by a DNA sequence in a clone deposited with Collection Nationale de Cultures de Microorganisms under accession number I-2706 which binds to RIP, (5) *any* composition comprising any polypeptide mentioned above and a pharmaceutically acceptable carrier for treating *any* disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only one polypeptide comprising the amino acid sequence of SEQ ID NO: 2 potentially encoded by a DNA sequence in a clone deposited with Collection Nationale de Cultures de Microorganisms under accession number I-2706 for blocking Jun kinase induction caused by RIP (See page 86 of the specification). The specification on page 86, line 5-7 discloses that RAP **was incapable** of binding to any of the known intracellular signaling proteins such as MORT-1/FADD, TRAF1, TRAF2, MACH, Mch34, and G1 mentioned above, including the irrelevant control proteins, such as lamin and cyclin D. The specification further discloses the following biological activities (i) RAP is not toxic to cells on its own when overexpressed, (ii) RAP does not protect cells from TNF killing, (iii) RAP does not induce NF-

κB on its own, (iv) RAP does block NF-κB activation by TRADD, RIP and p55 TNF-R and (v) blocks Jun kinase induction caused by RIP (See page 87 of the specification).

The specification does not teach how to make much less how to use *any* polypeptide fragment, analog, derivative mentioned above for treating any disease because binding or association does not equate to having a specific biological function, not to mentioned modulating *any* intracellular activity. There is insufficient guidance and working example that any fragment, any analog and derivative thereof of the polypeptide which is capable of binding to RIP encoded by deposited clone is capable of binding to RIP, much less modulate *any* intracellular activity as broadly as claimed because the term "modulating" can be increasing or decreasing. Further, it is not clear which intracellular activity is within the scope of the claimed invention. With regard to analog, there is no guidance as to which ten amino acid within the full-length polypeptide that has 522 amino acids encoded by the deposited clone can be substitute, delete, or insert and whether after modification will maintain both structure and functional biological activity such as inhibiting Jun kinase induction or blocking NF-kappaB activation by TRADD, RIP and p55 TNF-R pathways, in turn, would be useful to any disease.

Lin *et al*, of record, teach a variety of signals induce activation of NF-kappaB (See page 5899, column 1, first full paragraph, in particular) and RIP plays a structural rather than an enzymatic role in the TNFα response (See page 5899, column 2, last paragraph, in particular).

Kim *et at*, of record, teach a single amino acid change from D to A at position 324 of RIP (RIPD324A) activates NF-kappaB activation while ectopic expression of proapoptotic C-terminal fragment of RIP inhibited TNF-induced NF-kappaB activation (Abstract, in particular). Given the unpredictable nature of the function associated with polypeptide analog, it would take undue amount of experimentation to practice the claimed invention. Further, the specification discloses only **one** polypeptide of SEQ ID NO: 2. There are no additional polypeptide, fragment, analog and derivative thereof that have been demonstrate to be useful for modulating such as inhibiting or enhancing which intracellular activity of RIP, in turn, for treating any disease. Given the indefinite number of analog, derivative and fragment thereof, the insufficient guidance and working examples, predicting what changes can be made to the amino acid sequence of SEQ ID NOS: 2, which encoded by that after substitution, deletion, insertion and/or modification will retain both structure and have similar function requires guidance.

With regard to "derivative", not only the analog and fragment of any polypeptide which capable of binding to RIP and "modulating" or mediating any intracellular activity of RIP are not

enabled, there is insufficient guidance as to the kind of modification of *which* functional group, or N- or C-terminal group of any one or more amino acid of any polypeptide encoded by the deposited clone, fragment and analog thereof would maintain the same structure, much less binding to RIP. Let alone "modulate" any intracellular activity. Applicant has not provided sufficient guidance biochemical information (e.g. the amino acid to be substitute, the position within the full-length polypeptide to be substitute, delete, or add, etc.) that distinctly identifies the fragment, the analog and derivative that not only bind to RIP but also "modulate" any intracellular activity, other than the polypeptide encoded by the deposited clone. Even if the polypeptide is limited to full-length polypeptide, there is insufficient guidance as to which particular intracellular activity is to be increase or decrease. "It is not sufficient to define the fragment, analog or derivative by its principal biological activity, e.g. capable of binding to RIP, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property." Colbert v. Lofdahl, 21 USPQ2d, 1068, 1071 (BPAI 1992). Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Without sufficient guidance, the fragment, analog, derivative as well as composition comprising said fragment, analog or derivative and pharmaceutically acceptable carrier, that would, *in vivo*, be "capable of binding to RIP and modulating mediating the intracellular activity of RIP" is unpredictable, and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Regarding "composition" for "modulating" a*ny* intracellular activity of "RIP" comprising *any* fragment, *any* analog, and *any* analog of *any* fragment of RIP-associated protein mentioned above, there are no in vivo working examples in the specification to demonstrate that any fragment, analog and derivative mentioned above have *any* in vivo activity. A "pharmaceutical composition" in the absence of in vivo data are unpredictable for the following reasons: (1) the polypeptide fragment, analog, and/or derivative thereof may be inactivated before producing an effect, i.e. such as proteolytic degradation; (2) the polypeptide fragment, analog, and/or derivative thereof may not reach the target area because, i.e. the polypeptide fragment, analog, and/or derivative thereof may target to elsewhere for degradation, or has no effect; and (3) other functional properties, known or unknown, may make the polypeptide fragment, analog, and/or derivative thereof unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992). Since *any* amino acid sequence that comprises

"a fragment" of SEQ ID NO: 2, an analog of a RIP-associated protein (RAP) and an analog of a fragment of a RIP-associated protein are not adequately enabled, it follows that a composition comprising said fragment, analog, and derivative thereof and a pharmaceutical composition is not enable. Other than the specific polypeptide mentioned above for blocking Jun kinase induction caused by RIP and NF-κB activation by TRADD, RIP and p55 TNF-R *in vitro*, the specification does not teach how to make and use *any* fragment, *any* analog, *any* analog of *any* undisclosed fragment because there is no structure associated with the term "fragment", "analog" and derivative without the specific amino acid sequence.

For these reasons, the specification as filed fails to enable even one skill in the art to practice the invention without undue amount of experimentation. As such, further research would be required to practice the claimed invention.

Applicants' arguments filed 12/16/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) claims 13, 15 and 16 have been amended. (2) claim 13 now recites analogs having no more than ten amino acid substitution, deletions or additions and the analog must bind to RIP; the claimed analogs have a minimum of greater than 98% identity to the specified sequence. (3) the fragment, analog and derivative of claim 13 all require to have the ability to bind to RIP; Applicants concede that there is not 100% predictability in this field, as long as it is not shown that the experimentation is not undue, the enablement is met. When changing the sequence is less than 2%, there would be an expectation that the function is maintained. (4) while there are no working examples given in the specification for analogs, fragments, and derivatives, the specification provides guidance for yeast two-hybrid binding assay. The assays for binding are routine.

In response to Applicant's argument to items 1-4, the specification merely mentioned the term fragment, analog and derivative. The specification does not teach how to make, much less how to use fragment, analog and derivative mentioned above for treating any disease because binding does not equal to having a specific biological function, not to mentioned modulating *any* intracellular activity. There is insufficient guidance as to which ten amino acid within the full-length polypeptide that has 522 amino acids encoded by the deposited clone can be substitute, delete, or insert and whether after modification will maintain both structure and functional biological activity, in turn, useful for treating just any disease. There is no working example that any fragment, any analog and derivative thereof of the polypeptide which is capable of binding to

RIP encoded by deposited clone is capable of binding to RIP, much less modulate *any* intracellular activity as broadly as claimed because the term "modulating" can be increasing or decreasing. Further, it is not clear which intracellular activity is within the scope of the claimed invention. Kim *et at*, of record, teach that even a single amino acid change from D to A at position 324 of RIP (RIPD324A) affects its activity such as activating NF-kappaB activation while ectopic expression of proapoptotic C-terminal fragment of RIP inhibited TNF-induced NF-kappaB activation (Abstract, in particular). The specification discloses only **one** polypeptide of SEQ ID NO: 2. Although the specification provides binding assay such as yeast two hybrid, binding is not equivalent to biological function, let alone modulating any intracellular activity.

Applicant has not provided sufficient guidance biochemical information (e.g. the amino acid to be substitute, the position within the full-length polypeptide to be substitute, delete, or add, etc.) that distinctly identifies the fragment, the analog and derivative that not only bind to RIP but also "modulate" any intracellular activity, other than the polypeptide encoded by the deposited clone. Even if the polypeptide is limited to full-length polypeptide, there is insufficient guidance as to which particular intracellular activity to be increase or decrease. "It is not sufficient to define the fragment, analog or derivative by its principal biological activity, e.g. capable of binding to RIP, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property." Colbert v. Lofdahl, 21 USPQ2d, 1068, 1071 (BPAI 1992). Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Without sufficient guidance, the fragment, analog, derivative as well as composition comprising the fragment, analog or derivative and pharmaceutically acceptable carrier, that would, *in vivo*, be "capable of binding to RIP and modulating mediating the intracellular activity of RIP" is unpredictable, and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(e) the invention was described in-
(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or

(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

10. Claims 13, 15 and 16 stand rejected under 35 U.S.C. 102(e) as being anticipated by US Pat No 6,232,081 (May 2001, PTO 892).

The '081 patent teaches an isolated polypeptide which has the amino acid sequence such as LPLELKLRIFRLLDVRSVLSLSAVCRDLFTASNDPLLW, which is a fragment of the claimed polypeptide of SEQ ID NO: 2 encoding by a DNA clone under the accession number I-2706 (See SEQ ID NO: 47 of '081, column 2, lines 30-32, in particular). The functional properties of the reference fragment such as capable of inhibiting the NF-κB inducing effect of RIP or induction of NF-κB activity protects cell against TNF-mediated cell death is an inherent properties of the reference fragment because the claimed fragment of RIP appears to be the same as the reference fragment (See entire document, column 41, lines 44-45, in particular). The '081 patent teaches compositions comprising the reference protein and methods for development of drugs that disrupt at least one pathway in which the reference proteins function to ameliorate the effects of inflammatory response (See column 4, lines 37-50, in particular). Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 12/16/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) the present application has an effective filing date of the parent PCT application that has an effective filing date as early as March 19, 1998. The Harper patent filed Oct 15, 1998 and which is a CIP of another application filed Oct 1998.

However, the effective filing of instant application is 9/20/1999 because it is a CIP of 09/381,358. Further, the polypeptide which has the amino acid sequence such as LPLELKLRIFRLLDVRSVLSLSAVCRDLFTASNDPLLW of the '081 patent has supported in the parent (See page 95, SEQ ID NO: 47 of 08/951,621).

11. Claim 14 stands objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

12. No claim is allowed.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

15. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Phuong N. Huynh, Ph.D.
Patent Examiner
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February 24, 2003

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